

BRIEF COMMUNICATION

Absence of effect of somatostatin analogue (SMS 201-995) in diarrhea associated with inflammatory bowel disease

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ABSTRACT: The octapeptide long acting somatostatin analogue, SMS 201-995 promotes intestinal fluid and electrolyte absorption and inhibits anion secretion. It is more potent than native somatostatin and does not exhibit tachyphylaxis. SMS 201-995 was used to treat two patients with severe diarrhea associated with Crohn's disease after other treatments had failed. The volume and frequency of ileostomy output in one patient and stool output in the other did not respond to therapy with SMS 201-995. In fact, diarrhea appeared to increase in both patients while on treatment. *Can J Gastroenterol* 1989;3(2):53-57

Key Words: SMS 201-995, Absorption, Diarrhea, Inflammatory bowel disease, Intestine, Somatostatin analogue

Absence d'effet de l'analogue de la somatostatine (SMS 201-995) dans la diarrhée associée à la maladie inflammatoire de l'intestin

RESUME: L'analogue octapeptide à effet prolongé de la somatostatine, le SMS 201-995 (Sandostatine) favorise les fluides de l'intestin et l'absorption électrolytique et inhibe la sécrétion d'anions. Il est plus puissant que la somatostatine naturelle et ne produit pas de tachyphylaxie. Le SMS 201-995 a été utilisé dans le traitement de deux patients souffrant de diarrhée sévère associée à la maladie de Crohn après que tous les autres médicaments ont échoué. Le volume et la fréquence de l'écoulement de l'iléostomie chez l'un d'eux et des selles chez l'autre n'a pas réagi à la thérapie au SMS 201-995. En fait, la diarrhée semble avoir empiré dans les deux cas au cours du traitement.

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IN VITRO, LONG ACTING SOMATOSTATIN Analogue SMS 201-995 (Sandostatine; Sandoz Inc) has an antisecretory effect on intestinal electrolyte transport similar to native somatostatin. That is, it inhibits electrogenic anion secretion and stimulates neutral sodium and chloride absorption (1). Furthermore, this anti-diarrheal effect of SMS 201-995 is approximately 60 times more potent than native somatostatin and it does not exhibit tachyphylaxis (1). Clinically, SMS 201-995 has been used to control life threatening diarrhea due to colonic pseudo-obstruction (2), cryptosporidia infection in a patient with AIDS (3,4), idiopathic secretory diarrhea in an infant (5), idiopathic diabetic diarrhea (6), vasoactive intestinal peptide secreting tumours (7-11) and short bowel syndrome (12,13).

This report describes two patients treated with SMS 201-995 for diarrhea due to Crohn's disease. In both patients fecal output and stool frequency failed to improve and tended to increase during SMS 201-995 therapy.

CASE PRESENTATIONS

Case number 1: The patient was a 62-year-old caucasian female who had

suffered profuse ileostomy output since May 1985.

In 1944, the patient developed a perirectal abscess and underwent three surgical drainage procedures. Subsequently, severe incontinence developed as a result of anal sphincter disruption. The incontinence was treated in 1960 with a total colectomy and Brooke ileostomy.

After surgery, the patient was free from symptoms until late 1980 when she noticed the onset of abdominal cramps and increased liquidity of the ileostomy effluent. In March 1985, high output ileostomy losses resulted in hospitalization for severe volume depletion. Following rehydration with intravenous fluids she was discharged, however, her symptoms soon recurred.

In May 1985, the patient was again hospitalized with volume depletion secondary to high ileostomy output. Ileoscopy demonstrated a limited 50 cm segment of acute ileitis with histologic findings compatible with Crohn's disease. In September 1985, 50 cm of ileum was removed with revision of the ileostomy. Nevertheless, diarrhea continued with repeated hospital admissions for volume depletion requiring intravenous rehydration. In September 1987, ileoscopy demonstrated 50 cm of active Crohn's disease with normal small intestinal mucosa above this point.

Ileostomy output of 4000 g/day was reduced to 200 g/day using oral replacement solution (Gastrolyte, Rorer) on a v/v replacement schedule. Further investigations failed to identify an etiology to explain the high ileostomy output (Table 1). Therapeutic trials of lactose free diet, low fat diet, metronidazole, tetracycline, cholestyramine, loperamide, diphenoxylate, codeine, anticholinergic agents, Metamucil (G.D. Searle), 5-aminosalicylic acid, steroids and azathioprine failed to improve ileostomy output.

The patient was then placed on SMS 201-995 in an attempt to control the high volume ileostomy output.

Case number 2: The patient was a 30-year-old caucasian male with Crohn's ileal colitis who had suffered from continuous profuse watery diarrhea up to 12 times daily since 1981. He was initially treated with prednisone and salazopyrin,

TABLE 1
Diarrhea Investigation profile

Test	Case 1	Case 2
Stool volume		
Regular diet	1850 mL/day	545 mL/day
Fasting	750 mL/day	540 mL/day
Fat (0-20mmol/L)	199 mmol/day	62 mmol/day
Osmolality	474 mmol/kg	—
Na/K/Cl	101/34/73 mmol/L	—
Guaiac	Negative	Negative
Reducing sub	Negative	Negative
pH	6.4	—
NaOH reaction	Negative	Negative
Bile acids (0.2-1.0)	—	4.68 mmol/day
Culture	Negative	Negative
Ova and parasites	Negative	Negative
<i>Clostridium difficile</i> toxin	Negative	Negative
Blood		
Na/K/Cl/HCO ₃	Normal	Normal
Immunoglobulins	Normal	Normal
T ₄ , T ₃ RU	Normal	Normal
AST	Normal	Normal
Folate	Normal	Normal
Vitamin B12	Normal	Normal
Gastrin	Normal	Normal
Cortisol	Normal	Normal
Magnesium	Normal	Normal
Eosinophil count	Normal	Normal
Special assays		
VIP	Negative	Negative
Urine		
5-HIAA	Negative	Negative
X-rays		
SBFT	Crohn's disease	Normal
Abdominal sonogram	Normal	Normal
Small bowel studies		
Jejunum biopsy	Normal	Normal
Lactose breath H ₂	Normal	Normal
Upper endoscopy	Normal	Normal
Therapeutic trials		
Lactose-free diet	No benefit	No benefit
Low fat diet	No benefit	No benefit
Metronidazole	No benefit	No benefit
Antibiotics	No benefit	No benefit
Cholestyramine	No benefit	No benefit
Antidiarrheals	No benefit	No benefit
Anticholinergic	No benefit	No benefit
Metamucil/bulk agents	No benefit	No benefit
Corticosteroids	No benefit	No benefit

T₄ Thyroxine; T₃RU Triiodothyronine resin uptake; VIP Vasoactive intestinal peptide; 5-HIAA 5-Hydroxy indolacetic acid; SBFT Small bowel follow through; AST Aspartate aminotransferase

however, he continued to have eight to 12 bowel movements per day.

In March 1983, colonoscopy demonstrated scattered aphthous ulcers in the transverse colon and an acute distal ileitis extending proximally 10 cm. Stool volume was documented at 2500 g/day. The patient was treated with prednisone, salazopyrin and metronidazole.

In April 1985, the patient continued to have five to 10 bowel movements dai-

ly with stool volumes of 500 g/day. Colonoscopy and ileoscopy failed to demonstrate macroscopic or histologic evidence of active Crohn's disease. Further investigations failed to identify a specific etiology for the diarrhea (Table 1). A therapeutic trial of cholestyramine resulted in a temporary, four month improvement in symptoms. Nevertheless, the diarrhea returned and therapeutic trials of lactose free diet, low fat diet,

metronidazole, tetracycline, diphenoxylate, loperamide, codeine, anticholinergic agents. Metamucil and steroids failed to improve symptoms.

It was decided to start the patient on SMS 201-995 in an attempt to control his severe diarrhea.

MATERIALS AND METHODS

SMS 201-995 is a synthetic octapeptide with the structure D-phenylalanyl-L-hemicystyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-L-hemicystyl-L-threoninyl acetate.

After the patient gave informed consent, the drug (100 µg SMS 201-995 dissolved in 1 mL acetate buffered sodium chloride pH 4.0) was administered subcutaneously at 09:00 and 21:00 each day. The initial dose was 25 µg bid and was increased in steps of 25 µg bid at two day intervals until a maximal dose of 250 µg bid was reached. This dose was maintained for 30 days, after which SMS 201-995 was slowly withdrawn over 72 h. A 14 day drug-free interval followed and SMS 201-995 was restarted for an additional 30 day period.

Stool output was collected in pre-weighed containers (Sage Products, Cary, Illinois) and weights of the containers recorded by the patient with a scale supplied by the investigators. Stool weight, frequency, consistency and food intake were recorded daily in a diary. The diary began 14 days prior to drug administration and continued for the study dura-

tion. To ensure compliance, one of the investigators communicated by telephone with the patient three times weekly. The patients and their diaries were reviewed every two weeks in the gastroenterology research clinic, University of Alberta, Edmonton, Alberta.

During treatment with SMS 201-995, measurements of serum electrolytes, blood urea nitrogen, carotene, glucose, calcium, phosphate, total protein, albumin, cholesterol, uric acid and complete blood count were obtained at baseline, once during the first week of the study and then monthly.

RESULTS

The effect of SMS 201-995 on mean stool weight and frequency is shown in Figures 1 and 2 for cases 1 and 2, respectively. In both patients, there was no significant change in stool weight or stool frequency. Nevertheless, there was a trend towards worsening of stool output in both patients while on SMS 201-995.

Both patients complained of mild irritability which resolved spontaneously when the drug was removed. There was no alteration in the measured biochemical parameters and while weight remained stable in the first patient, a loss of 5 kg was documented in the second patient.

DISCUSSION

This study demonstrated that SMS 201-995 given by subcutaneous injection

did not alter stool weight or frequency in a patient with Crohn's ileal colitis nor in another with Crohn's ileitis and an ileostomy. Indeed, there was a trend towards worsening of stool output with an associated 5 kg weight loss in one patient.

SMS 201-995 is significantly more potent *in vitro* as an intestinal antisecretory agent than native somatostatin (1). This finding, along with the ability to administer SMS 201-995 subcutaneously, has led it to the forefront of potential anti-diarrheal agents. Despite early enthusiasm, this study suggests that SMS 201-995 may not be effective in severe diarrhea associated with inflammatory bowel disease (IBD).

Recently, intravenous infusion of SMS 201-995 reduced ileostomy output in five patients with severe ileostomy diarrhea, however, when administered subcutaneously ileostomy output in three of these five patients was not significantly improved (12). This may be explained by a lower effective concentration of SMS 201-995 at the level of intestinal enterocytes during subcutaneous injection. Nevertheless, increasing the frequency and total dose of SMS 201-995 failed to reduce ileostomy output (12).

The malabsorption of fat which is known to occur with somatostatin (12,14) may further aggravate the diarrhea in patients with IBD and precipitate weight loss. Although fat excretion was not measured while on SMS 201-995, fat malabsorption may be one mechanism to

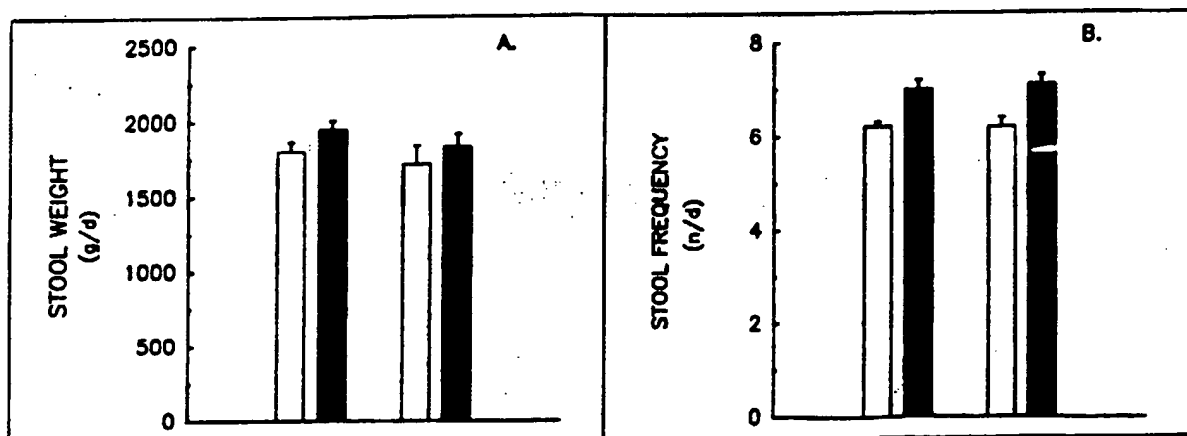


Figure 1) Effect of SMS 201-995 on ileostomy output in a patient (case 1) with small intestinal Crohn's disease. A Stool weight and B Stool frequency were measured continuously during two consecutive cycles of a 14 day drug-free interval (open bars) followed by a 30 day SMS 201-995 (250 µg bid) treatment interval (solid bars). Values represent mean \pm SEM

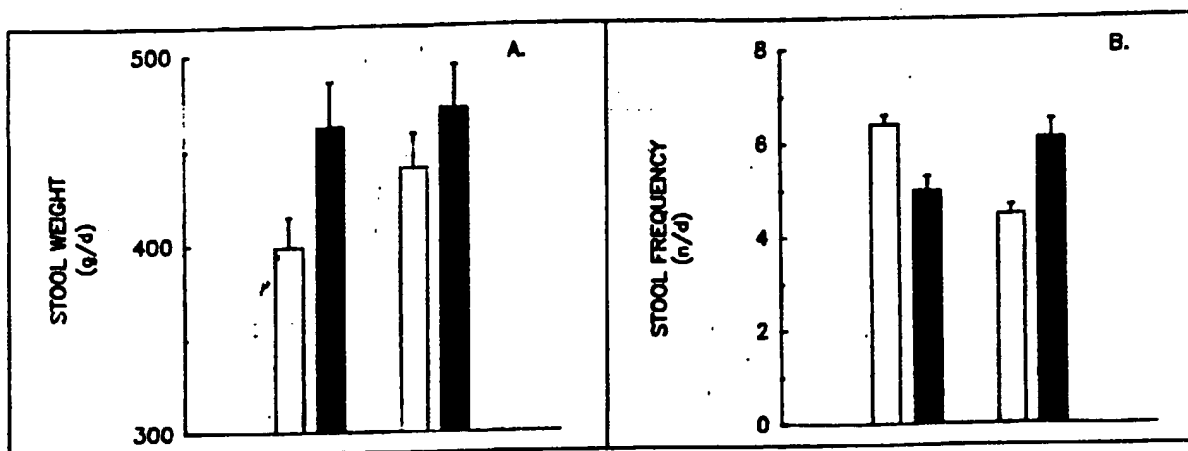


Figure 2) Effect of SMS 201-995 on fecal output in a patient (case 2) with ileal colonic Crohn's disease. A Stool weight and B Stool frequency were measured continuously during two consecutive cycles of a 14 day drug-free interval (open bars) followed by a 30 day SMS 201-995 (250 µg bid) treatment interval (solid bars). Values represent mean ± SEM

explain the trend towards increased stool output.

Recently, Clements and Elias (15) reported an adult patient with pancreatic cholera and metastatic VIPoma who had a delayed clinical and biochemical response to SMS 201-995 after one month of treatment. Although the patients in the present study continued SMS 201-

995 for a 30 day period, one of the patients (case 1) continued the SMS 201-995 off study for 60 consecutive days without reduction in stool output.

The major therapeutic benefit of SMS 201-995 remains in treating patients with acromegaly and gastrointestinal endocrine tumours (6-10,16-24). Its efficacy as an antidiarrheal agent for nonhor-

monally mediated secretory diarrheas is at best intermittent. The recent development of an aqueous solution of SMS 201-995 with rapid absorption of the gastrointestinal tract after local application may prove beneficial in delivering greater concentrations to the enterocyte and hence improve the clinical antidiarrheal action of SMS 201-995 (25).

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ABSTRACTS

Association between invasiveness, inflammation, desmoplasia and survival in colorectal cancer

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A multivariate analysis was used to test the prognostic importance of invasiveness, inflammatory reaction and amount of fibrous tissue at the tumour edge in 527 colorectal carcinomas. Allowance was made for clinicopathological stage, tumour site, histological type and grade. A poorly defined tumour border, lack of inflammatory reaction and pronounced desmoplasia at the tumour edge were all associated with unfavourable stage distribution and each of these features had an independent effect on prognosis.

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Review of GI disorders related to diabetes mellitus

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Gastrointestinal disorders are extremely common in patients with diabetes mellitus; prevalence rates of 30 to 75% have been recorded. The most common disorders are gastroparesis, diarrhea and constipation. Symptoms range from

mild to severe, with the most severely affected patients being at risk for protein calorie malnutrition. This paper presents an historical review of the major studies in this area as well as guidelines for nutritional assessment. Current methods for treatment of diabetic gastroparesis and related disorders are included with emphasis on nutritional support techniques. Practical outlines for glucose control in patients on total parenteral nutrition or enteral feeding and guidelines for transition from parenteral to oral diet are presented.

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Vertical gastric plication for gastroesophageal reflux

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An operation has been devised to prevent gastroesophageal reflux in which a vertical partition is made parallel to the proximal gastric lesser curvature. This simple technique (in which the stomach is neither opened nor divided) prevents reflux by: increasing the effective length of the intra-abdominal esophagus; increasing the crural sling and mucosal flap valve effect; sharpening the angle of entry into the gastric reservoir; and creating a flutter valve and markedly reducing cross-sectional area along which reflux can occur. Animal experiments and results from 26 patients who underwent this operation are discussed.

ANN R COLL SURGEONS (ENGLAND) 1989;71:31-6